REMARKS

By this amendment, Applicants have amended claims 32, 39, 56 and 59 to include embodiments where the single nucleotide polymorphic site comprises a single nucleotide polymorphism and the polymorphic site is immediately flanked by a 3' and 5' invariant nucleotide sequence. Claim 60 has been amended to include that the mammal is a horse. Support for these amendments can be found in the specification, for example, at page 11, lines 5-16, page 12, lines 5-8, Table 1 and Figure 6.

Applicants have also added new claim 61, which includes embodiments where the likelihood that a mammal is or is not an offspring of a putative parent mammal is determined by, among other things, comparing 18 polymorphic sites that have been separately (not simultaneously) sequenced. Support can be found, for example, in Examples 4 and 5 of the specification. No new matter has been added. Applicants respectfully request entry of this amendment and reconsideration of the application.

Rejection under 35 U.S.C. §112, First Paragraph: Written Description

The Examiner rejected claims 32-60 under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The written description requirement is satisfied where an invention is described in sufficient detail such that a person of ordinary skill in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). The disclosure should reasonably convey to a person of ordinary skill in the art that the inventor had possession of the subject matter in question. *Fujikawa v. Wattanasin*, 93 F.3d 1559 (Fed. Cir. 1996). If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, then the written description requirement is met even if every nuance of the claims is not explicitly described in the specification; the Examiner's burden is to provide reasons why a person of ordinary skill in the art would not consider the description sufficient. *In re Alton*, 76 F.3d 1168 (Fed. Cir. 1996). The

Examiner has the burden of presenting evidence or reasons why a person of ordinary skill in the art would not recognize that the written description provides support for the claims. *Revised Interim Guidelines for Examination of Patent Applications Under 35 U.S.C. § 112, Paragraph 1*, 64 FR 71427. Applicants respectfully submit that the Examiner has not met this burden.

The Examiner asserts that claim 32 has been interpreted as encompassing an "infinite number of single nucleotide polymorphisms in any and all regions of the genome of any mammal" (Office Action, Item 6).

Claim terms should be accorded their ordinary meaning to one of ordinary skill in the art. *See In re Morris*, 127 F.3d 1048 (Fed. Cir. 1997) and *Phillips v. AWH Corp*'s (Fed. Cir. 2005) (*en banc*). Applicants respectfully disagree with the Examiner interpretation of claim 32 and submit that one of ordinary skill in the art would not interpret the claims in the manner the Examiner described.

First, claim 32 is directed to identifying two or more single nucleotide polymorphic sites, wherein each polymorphic site comprises a single nucleotide polymorphism (SNP). The polymorphic site is immediately flanked by a 3' and 5' invariant nucleotide sequence. Thus "an infinite number of single nucleotide polymorphisms" are not claimed as the Examiner asserts. Second, the comparison step in the claims includes comparing SNPs that correspond to the same location (locus) on the genome. Thus, Applicants respectfully disagree with the Examiner's interpretation that "any and all regions of the genome of any mammal" are claimed. Third, the claims include that the comparison is among mammals of the same species. Thus comparisons of SNPs in monkeys and humans are not encompassed by the presently pending claims. Accordingly, Applicants submit that the Examiner is not interpreting the claims as one of ordinary skill in the art would, and the Examiner has not met his burden of showing that the inventors did not have possession of the invention at the time of filing.

Claim 56 requires the comparison to be performed in horses of the same breed; claim 59 requires comparing SNPs in upper and lower strands of DNA; and claim 60 specifically claims SNPs in at least one of SEQ ID NOs: 1-72. Thus, the Examiner's

position that an "infinite number of single nucleotide polymorphisms in any and all regions of the genome of any mammal" are claimed is untenable.

Further, the Examiner asserts that the claims include "identifying in a simultaneous manner any number of individuals" (Office Action, page 8, item 8). Applicants respectfully submit that the Examiner is using improper hindsight to interpret the claims by requiring disclosure for "simultaneous sequencing" in the specification—a technology that was not invented until about 2002 (see attached Murphy *Am. J. Pathology* 2002 July; 16(1):27-33), which is well after the filing date of the present application. Further, one of ordinary skill in the art would not interpret the claims as encompassing "simultaneous sequencing." Nevertheless, to expedite allowance Applicants have added new claim 61, which includes that the identification of SNPs is done separately—not simultaneously.

The Examiner also alleged that "six examples do not provide adequate written description of the claimed method where one would be able to determine any and all single nucleotide polymorphisms in any and all species of mammal" (Office Action, page 8, item 9).

Applicants have amended the claims to include that polymorphic site is immediately flanked by a 3' and 5' invariant nucleotide sequence. Thus, the presently claimed methods utilize specific types of SNPs at the same corresponding location on the genome or locus. Moreover, Examples 1-5 alone utilizes 18 polymorphic loci in sixty horses, which utilizes over 1,000 SNPs in the method described in the specification. Applicants submit the specification provides adequate written description and shows that the inventors were in possession of the claimed invention.

The specification at pages 13-15, page 44, lines 29-36 and Examples 1-6 clearly describe conducting genetic analysis using SNPs from mammalian DNA obtained from mammals of **the same species**. The application as filed satisfies the written description requirement because it unambiguously conveys to those of skill in the art that the Applicants were in possession of the claimed invention as of the priority date.

Applicants' insight that combinations of SNPs would be extremely useful as genetic markers and can be used for genetic analysis is a novel, useful, and nonobvious

application of their discovery regarding the distribution and density of SNPs in mammalian genomes. While the illustrative examples in the specification are directed to horses and humans, one of ordinary skill in the art upon reading the specification would readily understand that the methods and use of SNPs would be applicable to all species, including mammals of the same species. A person of ordinary skill would readily come to the same conclusion, and Applicants have described this applicability throughout their specification. Therefore, it is respectfully submitted that the specification fully complies with the written description requirement for methods of identifying single nucleotide polymorphic sites in the genome of mammals of the same species and using these SNPs to provide valuable genetic information including, among other things, determining allelic frequency, parentage, and identity among mammals of the same species. Accordingly, Applicants respectfully request withdrawal of this rejection.

Rejections Under 35 U.S.C. § 112, First Paragraph: Enablement

The Examiner rejected claims 32-60 under 35 U.S.C. §112, first paragraph for allegedly failing to comply with the enablement requirement. Applicants respectfully traverse this rejection.

The Examiner has the initial burden of presenting showing that the application does not teach how to make and use the invention. *In re Oetiker,* 977 F. 2d 1443 (Fed. Cir. 1992). Applicants respectfully submit that the Examiner has not met his burden.

The Examiner alleges that "the six examples provided do not set forth a reproducible procedure whereby one of skill in the art would be able to correctly associate a potential polymorphism with a given sequence when similar sequences are present yet belong to a **different species of mammal**" (Office Action, page 12, item 20, emphasis added).

Applicants respectfully disagree with the Examiner's interpretation of the claims and point out that one of ordinary skill in the art would not interpret the claims in the manner that the Examiner does. Claims 32-61 include methods for identifying single nucleotide polymorphic sites in the genome of mammals of the **same species**, not different species. Further, claims 49-50, 52, 55 and 60 are specifically directed to horses

and claims 56-58 are specifically directed to horses of the same breed. Thus, the Examiner's interpretation of the claims is untenable.

Applicants respectfully submit that the specification fully enables the claims. In the specification the inventors teach the advantages of using SNPs as genetic markers over other types of polymorphisms, including restriction fragment length polymorphisms (RFLPs), STRs (short tandem repeats), variable number tandem repeats (VNTRs). First, SNPs occur with greater allelic frequency and uniformity and thus can be linked to an individual trait (*e.g.*, to identify an individual, parentage, *etc.*). Second, SNPs are more stable than other classes of polymorphism's (*e.g.*, VNTRs, STRs, RFLPs) and are not typically subject to spontaneous mutation like other polymorphisms. Third, a SNP's allelic frequency can be inferred from a small number of representative samples. Fourth, SNPs allow a high degree of genetic information (*e.g.*, base position and location) unlike other types of polymorphisms (see the specification at pages 13-15).

At page 37-45, and Examples 4 and 5, the inventors teach how SNPs can be used to determine, among other things, parentage and identity. Although Examples 4 and 5 were conducted in horses, the same method can be conducted in mammals of the same species, and the specification clearly describes this, for example, at pages 4, lines 13-16, page 44 lines 29-36.

Applicants have also amended the claims to include that the polymorphic sites comprise a SNP, and the polymorphic site is immediately flanked by a 3' and 5' invariant nucleotide sequence and that the polymorphic sites correspond to the same location in the genome. Thus, the method utilizes specific types of SNPs at the same corresponding location or locus in the genome. Moreover, Examples 1-5 alone utilize 18 polymorphic loci in sixty horses, which amounts to over 1,000 SNPs utilized in the method. Applicants submit that the specification fully enables the claims. The specification at pages 13-15, page 44, lines 29-36 and Examples 1-6 clearly discloses and enables conducting genetic analysis using SNPs from mammalian DNA of the same species.

The Examiner asserts that the claims encompass "the simultaneous analysis of nucleic acid samples from virtually any and all mammals" (Office Action, page 14, item 26). Applicants respectfully submit that the Examiner is using improper hindsight to

interpret the claims by requiring disclosure for "simultaneous sequencing" in the specification—a technology that was not invented until about 2002 (see Murphy Am. J. Pathology 2002 July; 16(1): 27-33), which is well after the filing date of the present application and one of ordinary skill in the art would not interpret the claims in this way. Nevertheless, to expedite allowance Applicants have added new claim 61, which includes that the identification of SNPs is done separately—not simultaneously.

As previously argued in the prior response, the Examiner's reliance on *Genentech v. Novo Nordisk* ("*Genentech*") as analogous to the present case is misplaced. *Genentech* was decided on strikingly different facts. In *Genentech*, the claims recited a method for making human growth hormone in a fusion protein and cleaving the fusion protein to make the growth hormone. The patentees in *Genentech* tried to rely on the level of skill in the art to enable the claim, but at the time of filing the application it was ***not*** known in the art how to cleave a fusion protein to make growth hormone, ***where the cleaving of the fusion protein was the novel aspect of the claim***. In contrast, the novel aspect of the amended claims does not include claims to individual SNPs, but methods using the combinations of SNPs as useful genetic markers. Thus, *Genentech* sheds no light on any alleged written description or enablement issues with respect to the present claims. *Genentech* is simply inapplicable to the facts of this case.

Moreover, claims 59 and 60 have been added to include where the starting material involves known SNPs to determine the parentage testing. It is respectfully submitted that the starting material is clearly provided by the specification. Applicants submit that the specification fully complies with the enablement requirement for methods of identifying and characterizing single nucleotide polymorphic sites in the genome of mammals of the same species. Accordingly, Applicants respectfully request withdrawal of this rejection.

Rejection under 35 U.S.C. §112, Second Paragraph

The Examiner rejected claims 32-60 as allegedly indefinite for the phrase "single nucleotide polymorphic site " recited in the claims. Applicants respectfully disagree with the Examiner and submit that the claims are clear to a person of ordinary skill in the art

upon reading the specification. However, solely to expedite prosecution, Applicants have amended the claims to include that the single nucleotide polymorphic site contains a single nucleotide polymorphism and the polymorphic site is immediately flanked by a 3' and 5' invariant nucleotide sequence. Accordingly, Applicants request reconsideration and withdrawal of the rejections based on 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. §103(a)

The Examiner rejects claims 32-36, 38-43, 45-46,48, 51, 53, 54, and 59 under 35 U.S.C. §103(a) as allegedly being obvious over *Eur. J. Immonogenet.* 18:33-55 (1991) (Erlich). The Examiner also rejects claims 33-35 and 39-55 under 35 U.S.C. §103(a) as allegedly being obvious over Erlich in view of *Swiss Medical Weekly* 119:815-825 (1989) (Fey). Applicants respectfully traverse these rejections.

To establish a *prima facie* case of obviousness, all of the claim elements must be taught or suggested by the prior art. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir.1991). Applicants respectfully disagree with the Examiner's position and submit that neither Erlich nor Fey alone or in combination disclose, teach or suggest methods of using a panel of SNPs to determine allelic frequency, parentage and identity among mammals of the same species.

In the Office Action, the Examiner alleges that Erlich shows a method of identifying SNPs in a genome of interest, particularly in 18 different sequences (Office Action, item 35 on page 16). The Examiner refers to Figure 1-3 and Table 1 of Erlich in support of his position. Applicants respectfully disagree with the Examiner.

Erlich teaches typing the HLA gene using allele specific oligonucleotide probes (ASO) that hybridize to HLA class II polymorphisms DQA1, DQB1, DRB1, and DPB1. These HLA class II polymorphisms are polymorphic regions and not single nucleotide polymorphisms. The allele specific probes listed in Table 1, cited by the Examiner, do not discriminate among alleles that differ by a single nucleotide base. If the ASO probes did, they would differ by one nucleotide base as well. Figure 3, which the Examiner also cites, illustrates the DNA sequence and probe alignments for the probes listed in Table 2. Note the DNA locus and probe alignments listed in Table 2 of Erlich and the regions he

interrogates have multiple nucleotide variations and could not be—and are not—considered single nucleotide polymorphisms that are immediately flanked by a 3' and 5' invariant nucleotide sequence as currently claimed.

In contrast to SNPs, Erlich teaches polymorphic regions containing at least 2 to 3 nucleotide variations:

> The allelic diversity at the DPB1 locus presents more of a challenge for oligonucleotide probe typing because of the dispersed nature of the **polymorphic sequences** (Fig. 3). The second exon contains six variable regions (A to F) with a limited number of **polymorphic residues (n=2-3) at each position** (Erlich, at page 37, emphasis added).

Erlich's ASO probes each are directed against a specific allele having a polymorphic region that is arrayed and exposed to PCR amplicons generated by the sample, and it is the pattern on the array that reveals the genotype:

> Our approach has been to use a panel of 15 oligonucleotide probes (listed in Table 2) specific for the sequence variants in four polymorphic regions with the pattern of probe hybridization identifying a specific DPB allele (see Table 3). (Erlich, at page 40).

Thus, Erlich describes identifying patterns of matching ASOs with sample amplicons, where the amplicons are of polymorphic regions, not SNPs that identify genotypes. Accordingly, Erlich teaches trait association by polymorphic region, not by SNPs.

Fey, like Erlich, does not disclose, teach or suggest utilizing SNPs. Fey teaches two different types of polymorphisms: (1) RFLPs and (2) highly variable regions (HVRs)--which is a type of VNTR. These types of polymorphisms are discussed on pages 2 and 3 of the specification. And again, one of ordinary skill in the art would not consider these types of polymorphisms to be SNPs.

Moreover, Applicants submit that before the filing of the present application, one of ordinary skill in the art would not consider using a panel of SNPs as genetic markers and would not have recognized that SNPs could provide valuable genetic information

including, among other things, determining allelic frequency, parentage and identity among mammals of the same species.

Since neither Erlich nor Fey disclose, teach or suggest methods of using a panel of SNPs to determine, among other things, allelic frequency, parentage and identity among mammals of the same species, Applicants respectfully submit that the present claims cannot be considered obvious. Accordingly, Applicants respectfully request withdrawal of the rejections.

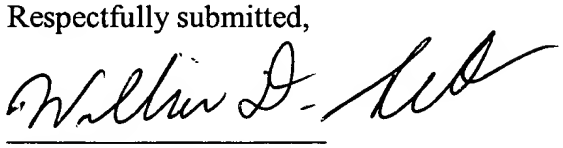
Conclusion

Reconsideration and allowance are respectfully solicited.

Applicants petition the Commissioner for 3-month extension of time and enclose the fee. If any additional fees are due, or an overpayment has been made, please charge, or credit, our Deposit Account No. 11-0171 for such sum.

If the Examiner has any questions regarding the present application, the Examiner is cordially invited to contact Applicants' attorney at the telephone number provided below.

Respectfully submitted,



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1: Am J Pathol. 2002 Jul;161(1):27-33.

Simultaneous sequencing of multiple polymerase chain reaction products and combined polymerase chain reaction with cycle sequencing in single reactions.

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DNA sequencing is considered the gold standard for nucleic acid identification and mutation detection. However, sequencing is labor intensive because it requires previous amplification and only a single sequence is analyzed at a time. We developed two novel strategies that substantially improve DNA sequencing. The first allows multiple polymerase chain reaction (PCR) products to be sequenced in a single sequencing reaction and analyzed simultaneously in a single lane or capillary. Simultaneous sequencing by this method, designated "SimulSeq," can provide either simultaneous single-direction sequencing of multiple genes or simultaneous forward and reverse sequencing from a single gene. In the second approach, designated "AmpliSeq," we demonstrate a technique combining PCR amplification and sequencing in a single reaction that is analyzed in a single lane or capillary. We demonstrate combined PCR with short bidirectional sequencing, and combined PCR with unidirectional sequencing. We anticipate that these methods will have utility in research and clinical settings where panels of mutations or large numbers of samples are be analyzed and/or when turnaround time is critical.

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